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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING BUPROPION HYDROCHLORIDE

(57) Abstract

A pharmaceutical composition in solid dosage form comprising bupropion hydrochloride as active drug and sodium bisulfate as stabilizer.

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PHARMACEUTICAL COMPOSITION COMPRISING BUPROPION HYDROCHLORIDE

BACKGROUND OF THE INVENTION

Bupropion hydrochloride is a well known antidepressant. It is sold in the United States by Glaxo Wellcome Inc. as prompt release tablets under the tradename WELLBUTRIN® and sustained release tablets under the tradename, WELLBUTRIN SR®.

Bupropion hydrochloride is known to be relatively unstable, such that tablets containing bupropion hydrochloride will degrade at an unacceptably high rate unless the tablets are made by a method or using ingredients which result in improved stability.

U.S. patent 5,358,970 discloses stabilization of bupropion hydrochloride by including in the tablets a stabilizer. The specific stabilizers disclosed are L-cysteine hydrochloride, glycine hydrochloride, ascorbic acid, malic acid, sodium metabisulfite, isoascorbic acid, citric acid, and L-cysteine hydrochloride. L-cysteine hydrochloride and glycerin hydrochloride are said to be most preferred. All of the examples in U.S. patent 5,358,970 use L-cysteine hydrochloride or glycine hydrochloride as the stabilizer, and, in each example, the process of manufacture includes the steps of dissolving the stabilizer in water and alcohol, using the solution to granulate the bupropion hydrochloride and other ingredients, and then drying the wet mass.

Such a process has the disadvantage of requiring the use of water and alcohol, and requiring the steps of preparing the solution, using the solution to granulate powder, and drying the wet granulated material.

The object of the present invention is to enable stabilization of compositions comprising bupropion hydrochloride by using a stabilizer other than that disclosed in U.S. patent 5,358,970.

DESCRIPTION OF THE INVENTION

It has been found that the inclusion of sodium bisulfate as an ingredient in solid compositions comprising bupropion hydrochloride results in improved stability, even if the ingredients are mixed in dry form without use of water, alcohol or any other solvent.

Compositions within the scope of the present invention will thus be solid compositions (such as tablets or capsules) comprising bupropion hydrochloride and sodium bisulfate. Sodium bisulfate is available as both anhydrous and monohydrate. Either form may be used in the present invention.

A preferred ratio of sodium bisulfate to bupropion hydrochloride by weight is from about 1 to about 20 parts sodium bisulfate per 100 parts bupropion hydrochloride. A more preferred ratio is from about 2 to about 10 parts sodium bisulfate per 100 parts bupropion hydrochloride. The most preferred ratio is about 5 parts sodium bisulfate per 100 parts bupropion hydrochloride.

Solid compositions in the form of tablets, for example, can be made simply by mixing bupropion hydrochloride and sodium bisulfate, along with other usual tabletting ingredients, and then compressing the mixture into tablets on a tablet process.

The other usual tabletting ingredients may include and will preferably include a binder, such as, for example, microcrystalline cellulose or hydroxypropyl methylcellulose; a lubricant such as, for example, magnesium stearate, zinc stearate, or stearic acid, and a glidant such as, for example, colloidal silicon dioxide.

If the flowability of the mixed powder is not adequate for direct compression into tablets, the mixture may be compacted, following which the compacted material will be ground up into free flowing granules. These granules will then be compressed into tablets on a tablet press.

The following examples are representative of the invention, but not limiting.

Ingredients were mixed in proportions as follows:

	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5
Bupropion hydrochloride	100.	100.	100	100	100.
Microcrystalline Cellulose	98.	96.	94.	90.	82.
Sodium Bisulfate, Monohydrate	0	2.	4.	8.	16.
Zinc Stearate	1.6	1.6	1.6	1.6	1.6
Colloidal silicon dioxide	0.4	0.4	0.4	0.4	0.4
	200.	200.	200.	200	200.

In each case, the powder mixture was compacted, the compacted material was ground up into granules, and the granules were recompressed on a tablet press into tablets of net weight 200 mg each. Each tablet thus contained 100 mg of bupropion hydrochloride, and the amount of sodium bisulfate per tablet was nil in example 1, 2 mg in example 2, 4 mg in example 3, and 8 mg in example 4, and 16 mg in example 5.

The tablets of all 5 examples were stored for a period of one week at 50°C, this condition of elevated temperature being known to cause accelerated degradation of bupropion hydrochloride.

At the end of the one week period, the tablets were analyzed to determine the total amount of degradation products as a percentage of the initial amount of bupropion hydrochloride. The total amount of degradation products was found to be over 25% for example 1 (which uses no sodium bisulfate), but only 2.89% for example 2, 0.26% for example 3, and 0.11% for examples 4 and 5.

It thus can be seen that the inclusion of sodium bisulfate in the tablets decreases the rate of degradation. Furthermore, the rate of degradation decreases with increased amount of sodium bicarbonate. In example 3, which comprises 4 parts sodium bisulfate per 100 parts bupropion hydrochloride, the rate of degradation is acceptably low, and it appears that there is thus little to be gained by using substantially above this level of sodium bisulfate. It is thus concluded that the most preferred ratio of sodium bisulfate to bupropion hydrochloride is about 5 parts sodium bisulfate to 100 parts bupropion hydrochloride.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition in solid form comprising bupropion hydrochloride and sodium bisulfate.

2. A composition of claim 1, comprising by weight from about 1 to about 20 parts sodium bisulfate per 100 parts bupropion hydrochloride.

3. A composition as in claim 2, comprising by weight from about 2 to about 10 parts sodium bisulfate per 100 parts bupropion hydrochloride.

4. A composition as in claim 3, comprising by weight about 5 parts sodium bisulfate per 100 parts bupropion hydrochloride.

5. A composition as in any of claims 1 to 4 in the form of a tablet.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/CA 99/01114

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/02 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 358 979 A (MICHAEL D. RUFF, ET AL.) 25 October 1994 (1994-10-25) cited in the application the whole document	1-5
P,A	WO 99 33456 A (AMERICAN HOME PRODUCTS) 8 July 1999 (1999-07-08) the whole document	1-5

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☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

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